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Analgesic effects of alcohol: A systematic review and meta-analysis of controlled experimental studies in healthy participants

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Abstract

Despite the long-standing belief in the analgesic properties of alcohol, experimental studies have produced mixed results. This meta-analysis aimed to clarify whether alcohol produces a decrease in experimentally-induced pain and to determine the magnitude of any such effect. PubMed, PsycINFO and Embase databases were searched from inception until 21/4/2016 for controlled studies examining the effect of quantified dosages of alcohol on pain response to noxious stimulation. Eighteen studies involving 404 participants were identified providing alcohol vs. no-alcohol comparisons for 13 tests of pain threshold (N=212) and 9 tests of pain intensity ratings (N=192). Random effects meta-analysis of standardized mean differences (SMD) provided robust support for analgesic effects of alcohol. A mean blood alcohol content (BAC) of approximately 0.08% (3-4 standard drinks) produced a small elevation of pain threshold (*SMD*=0.35[0.17, 0.54], *p*=.002), and a moderate-large reduction in pain intensity ratings, (*SMD*=0.64[0.37, 0.91], *p*<.0001), or equivalently, a mean reduction of 1.25 points on a 0-10 point pain rating scale. Furthermore, increasing BAC resulted in increasing analgesia, with each .02% BAC increment producing an increase of *SMD*=.11 for pain threshold and *SMD*=.20 for reduced pain intensity. Some evidence of publication bias emerged, but statistical correction methods suggested minimal impact on effect size. Taken together, findings suggest that alcohol is an effective analgesic that delivers clinically-relevant reductions in ratings of pain intensity, which could explain alcohol misuse in those with persistent pain despite its potential consequences for long-term health. Further research is needed to corroborate these findings for clinical pain states. ***Keywords****: pain, alcohol, ethanol, analgesia, review, meta-analysis*

Perspective

This meta-analysis provides robust evidence for the analgesic properties of alcohol, which could potentially contribute to alcohol misuse in pain patients. Strongest analgesia occurs for alcohol levels exceeding World Health Organisation guidelines for low-risk drinking and suggests raising awareness of alternative, less-harmful pain interventions to vulnerable patients may be beneficial.

1 Introduction

A link between increased alcohol use and reduced chronic pain has emerged from several large population-based studies. Macfarlane and Beasley[47] found that self-reported moderate-high (11-35 units/week) drinkers were approximately two-thirds as likely to report chronic widespread pain than infrequent drinkers. Furthermore, amongst those with pain, moderate-high drinkers were around a quarter as likely to report disabling pain. This relationship has been confirmed in a further study of chronic widespread pain[4] and extends to fibromyalgia[40] and knee pain[42]; although any putative benefits of alcohol disappear for extreme levels of consumption[72]. Moreover, the possibility that up to 25% of people with pain report self-medication with alcohol due to its perceived analgesic properties[56] is troubling given the health consequences of sustained alcohol use. However, while the relationship between pain and opiate misuse has been extensively studied, considerably less attention has been devoted to pain and alcohol use[17].

While these findings are suggestive of an analgesic effect of alcohol, causality cannot be determined from observational data and alternative explanations have been proposed. For example, chronic pain and alcohol dependence may share common neural circuits[17] and pain states could affect alcohol usage by influencing reward pathways that regulate consumption[2]. Alternatively, deterioration in pain may lead to reduced alcohol intake due to increasing health concerns or medication contraindications. Classification decisions of level of alcohol use and inaccurate self-reporting may further influence findings[41]. Fillmore et al.[18], for example, demonstrated that the link between alcohol use

and heart disease disappeared when reclassifying 'alcohol abstainers' to exclude former drinkers.

Understanding causal direction in the link between alcohol use and pain is important. If alcohol does produce analgesia, this may encourage alcohol dependence in those with pain[17], and suggests that efforts to promote alternative interventions for chronic pain with fewer negative health consequences (e.g. physical therapy, exercise, controlled administration of pain medication) may be worthwhile. The use of experimental pain paradigms can help determine causality by studying the impact of measured dosages of alcohol on quantifiable indices of pain in response to noxious stimuli, and avoids many of the confounds present in clinical data[58]. However, while experimental studies have offered some evidence for alcohol analgesia, findings are inconsistent and have exhibited substantial variation in effect sizes[34].

As such, our current understanding of alcohol analgesia is limited. This is perhaps surprising considering the long-standing acceptance of the analgesic properties of alcohol and claims of an analgesic potency comparable to opiates[36,69]. Given the general use of small samples and variability in dosages, administration methods and outcome measures in previous studies[34], our understanding of alcohol analgesia would be significantly advanced by meta-analysis of existing data to optimize power and provide robust estimates of effect size accounting for different sources of study heterogeneity.

We therefore conducted a meta-analysis of controlled experiments examining the impact of measured alcohol dosages vs. no-alcohol on response to noxious stimulation in human participants to determine the: (1) the existence of alcohol analgesia; (2) the magnitude of any analgesic effects; and (3) the impact of moderating variables.

2 Methods

This systematic review was conducted in accordance with the PRISMA-P 2015 statement for systematic review and meta-analysis protocols[51].

2.1 Eligibility Criteria

Studies were included that utilized: (1) adults given a controlled quantified dose of alcohol; (2) a comparative no-alcohol control group/condition; (3) medically and neurologically healthy participants; (4) an experimental pain stimulus and an established pain assessment (e.g., pain threshold); and (5) were published in an international peer-reviewed journal or conference abstract.

Studies were excluded if samples consisted of chronic pain patients or those with a history of alcohol abuse, as these may represent heterogeneous groups with altered processing of sensory or noxious stimuli[7].

2.2 Search Procedure

Two reviewers (CO, BS) independently searched PubMed, EMBASE, PsycINFO and CINAHL Plus from database inception until 21/4/2016 using the major

search terms (ethanol OR alcohol) and ((pain OR nociception) OR (analgesia OR analgesi*)) and a number of secondary search terms relating to experimental pain stimuli including 'pressure' or 'mechanical' or 'cold' or 'heat' (see Appendix S1 for details). Search results were refined using limits of human studies and English language. Additional studies were identified by manually searching the reference lists of all relevant articles.

2.3 Study selection

After removal of duplicates, two reviewers (CO, BS) independently screened titles and abstracts and developed a list of potentially eligible full text articles. Two authors (CO, BS) applied eligibility criteria and a final list of articles for inclusion was reached through consensus. Corresponding authors were contacted up to 3 times over a six week period to clarify results or to request additional data.

2.4 Pain outcomes

Multiple assessment measures of pain threshold, pain tolerance and pain rating scales were identified as outcomes, as these have been shown to be valid methods of quantifying pain that collectively capture different aspects of the pain experience[27]. Pain threshold is the minimum amount of stimulation that evokes a report of pain, and pain tolerance is the point of maximum endurance[27], and both are typically measured in time or stimulation intensity. While threshold involves low-intensity pain and is influenced primarily by sensory processes (e.g., localization and initial detection), tolerance concerns near-maximal pain and is

strongly influenced by affective mechanisms[1]. Pain rating scales provide an easily interpretable index of subjective pain and typically assess sensory (e.g., intensity) or affective (e.g., discomfort) dimensions of pain on a 0-10 self-report scale.

2.5 Study quality

Two raters (CO, NA) independently rated each study for methodological quality on a 13-item validity scale assessing methodological rigor, selection and reporting bias (Appendix S2). The scale was based on items from Cochrane collaboration criteria, PRISMA recommendations, PEDro guidelines as reported by Ditre et al.[11], and was adapted for studies examined in the current review.

2.6 Data Extraction

Two authors (CO, BS) independently extracted and coded study data on a standardized extraction form used in several of our previous studies[60,62] with a few minor adaptations for the current topic. Means and standard deviations of pain measures were recorded, along with other key statistical information from which effect size can be computed[46]. The following additional data were recorded for use in moderator analysis and to summarize study characteristics: sample (age, gender composition, weekly alcohol consumption, familial drinking history), alcohol manipulation (dosage, blood alcohol content % (i.e. g/dL), administration method), control group (inactive control/placebo), study design (within/between-groups), pain induction method (e.g., electrical, pressure) and pain outcomes.

A number of decisions were made when computing effect sizes from extracted data. (1) When a study reported data from multiple independent groups of participants (e.g., with/without a family history of alcoholism), effect sizes were computed for each subgroup and included in the meta-analysis as independent samples following the recommendations of Borenstein et al.[5]. (2) A few studies assessed pain multiple times in the same participants (k=3 studies reported multiple alcohol concentrations, k=1 study used multiple pain inductions). In these instances, a mean pooled effect size was calculated for the overall meta-analysis, with individual effect sizes also computed for different alcohol concentrations for use in moderation analysis. Effect size variance was calculated using the reported mean correlation of pain scores, or if not presented, using an imputed correlation of r=0.75[5]. This value was chosen as it represents a reasonably typical test-retest correlation[13], was reported by the study with the largest sample in the current meta-analysis[59] and approximates the correlation obtained from a pool of over 300 participants undergoing repeated pain testing in our own lab[61,63,64]. (3) For one study that reported an effect as significant at p<.001, a conservative effect size estimate was derived from rounding to p=.001. (4) For a few studies (k=2) that applied an experimental aggression paradigm, pain scores only from the 'low provocation' group were recorded to minimize any potential influence of this paradigm on group differences. (5) For one study that reported semi-IQRs rather than SDs, these were converted to SDs by applying a multiplication factor of 0.75 based on the assumption of normality[28].

2.7 Sensitivity analysis

Potential consequences of key decisions in the previous section were assessed with sensitivity analysis. In particular, the impact of using r=0.75 as the imputed correlation when study correlations had not been reported, was examined by repeating analyses using a wide range of alternative coefficients in .05 increments from r=0.30-0.90.

2.8 Meta-analysis

The standardized mean difference between alcohol and control groups was computed for each study using Hedges' g formula[5]. This is equivalent to Cohen's d, but with a correction for small sample bias, and can be interpreted in the same way, with .20, .50 and .80 roughly corresponding to small, medium and large effects[9]. Effect sizes were computed using the original (unadjusted) standard deviations for both within-group and between-groups designs[53]. Hedges' g was coded so that positive values indicated an analgesic effect of alcohol (i.e., increased pain threshold/tolerance or decreased pain ratings).

A random effects model was used as heterogeneity in effect sizes was likely given the methodological variation typically evident in experimental pain research[15]. Cochran's Q was used to assess the presence of heterogeneity and Higgins' I^2 and tau (τ) to quantify the extent of heterogeneity. I^2 estimates the proportion of total variation in effect size due to true heterogeneity, with values of 25%, 50% and 75% indicating possible low, moderate, and high heterogeneity[32], and τ estimates the standard deviation of the different population effect sizes.

Model parameters were estimated using restricted maximum likelihood with separate tests conducted for each outcome. Meta-analysis was only performed for outcomes when more than 5 studies were available, as fewer studies can lead to unreliable parameter estimates for random effects[35]. Pain ratings were only analyzed for studies where stimulation intensity was identical for both groups (i.e., where a fixed-intensity/fixed-time paradigm was used), to avoid confounding of any group differences in pain ratings with differences in stimulation intensity.

2.9 Publication bias

To assess whether overall effect size estimates could be potentially inflated by publication bias, funnel plots of study effect sizes against standard errors/sample size were examined. If the plot suggested asymmetry due to the absence of small sample studies with small effect sizes (i.e., those most likely to be non-significant), this suggests potential publication bias. Asymmetry was tested statistically with Egger's bias test[16], with $p<.05$ indicating asymmetry. If results were consistent with possible publication bias, a trim and fill method[14] was used. This involves estimating a revised effect size after trimming smaller (less precise) studies, and then filling in imputed values from the presumed missing studies to create a symmetrical plot and a more accurate estimate of variance.

2.10 Meta-regression

If heterogeneity was present and data were available for approximately 10 comparisons or more[33], meta-regression was conducted to examine whether the

effects of alcohol were influenced by several variables. Primary moderators were blood alcohol content (BAC) and drinking frequency (mean weekly alcohol consumption), with the rationale that both factors were likely to influence analgesic effects. Secondary moderators were gender composition, time between alcohol administration and pain testing, type of control (active placebo/passive control) and alcohol administration method, and were examined in an exploratory approach, in that it was determined *a priori* that any significant effects could only be considered preliminary. Study quality was also examined as a potential influence on effect size, with overall quality ratings and key individual design variables of counterbalancing and experimental blinding entered as moderators. Separate analyses were conducted for each moderator.

All analyses were performed using the metafor[66] package in R[54].

3 Results

3.1 Database searches

Initial database searches yielded 1816 unique hits with 7 potentially relevant records identified through manual searching of reference lists. Following screening of abstracts, 28 articles were retained for full text review. Three author groups were contacted to request clarification of or additional data and responses were received from all 3. Overall, of the 28 articles, 10 were excluded, with reasons for exclusion and a summary of the study selection process shown in Figure 1. Altogether, 18 studies were retained for analysis.

3.2 Study characteristics and study quality

The 18 retained studies comprised a total of *N*=404 participants and provided data for 22 group comparisons, as 3 studies[19,21,55] reported data for an additional 4 independent samples. Key study characteristics are presented in Table 1. Of the 18 studies, data were missing for mean weekly alcohol consumption (*missing k* =13), age (*k*=10), gender (*k*=3) and BAC (k=2), otherwise all key data were reported. The majority of studies (*k*=16; 89%) utilized a within-subjects design, 14 of which provided a minimum interval between testing of alcohol and control conditions of one day. Mean time between alcohol administration and pain testing was 42 mins (*SD*=17; range=15-90).

-- TABLE 1 ABOUT HERE --

The following number of independent alcohol vs. control comparisons was available for analysis: pain threshold (*k*=13, *N*=212), pain tolerance (*k*=3, *N*=62), pain ratings of intensity (*k*=9, *N*=192) and discomfort (*k*=5, *N*=137). As the number of comparisons available for tolerance and pain discomfort did not exceed 5[35], these outcomes are not considered further. The studies that provided pain threshold data were different to those that provided pain ratings, generally reflecting the experimental choice between a threshold and a fixed-stimulus paradigm, where stimulation intensity is fixed for all participants (4 of the 13 pain threshold studies also reported pain intensity ratings, but ratings from these studies were not included in analysis of pain intensity due to inherent

confounding with group differences in stimulus intensity - see Section 2.8) Study characteristics for these two sets of studies are presented in more detail in sections 3.2.1 and 3.2.2 below.

Ratings of study quality showed acceptable agreement across two raters for overall quality ratings, *ICC*(A,1)=0.75, and across individual items (*Kappa*=0.61-1.00) with 100% consensus reached where any disagreement had occurred. Mean overall study quality scores were high, *M*=9.9 (on a 0-13 scale), with most studies (89%) randomizing order/group allocation and 61% of studies employing subject/experimenter blinding (see Appendix S2 for all item ratings).

3.2.1 *Pain threshold*

The 13 independent comparisons for pain threshold consisted of 182 participants in the alcohol group/condition and 182 participants in the control group/condition (mean age=24.3 years, 79% male). Noxious stimulation was applied using a variety of modalities (electric=5, pressure=5 , chemical=2, heat=1). Two methods of alcohol administration were used (drink=7, intravenous=6), with studies providing alcohol administered through drink reporting a mean dosage of 1.07 ml/kg. Mean BAC at testing was 0.079% (range=0.058-0.110). Based on the inverse Widmark equation[67], this is roughly equivalent to 3-4 standard drinks at consumption time for a typical male, or 2-3 standard drinks for a typical female (where standard drink is based on the US definition of 14g ethanol, e.g., 1 x 150ml glass of 12% wine or 1 x 330ml glass of 5% beer, although definitions of a standard drink varies across countries[39]). Alcohol was compared with either a placebo/pseudoplacebo (*k*=4), usually a

negligible alcohol dose, or an inactive control (*k*=9). Overall study quality scores ranged from 6 to 12 (*M*=8.9, *SD*=2.02).

3.2.2 *Pain intensity ratings*

The 9 independent comparisons for pain intensity ratings consisted of 174 participants in the alcohol group/condition and 129 participants in the control group/condition (mean age=27.2 years, 98% male). Two stimulus modalities were used (electric=7, cold=2) to deliver noxious stimulation with a mean baseline pain intensity rated as 5.3 (*SD*=1.1) points on a 0-10 point scale. Alcoholic drink was the sole method of alcohol administration with a mean dosage of 0.94 ml/kg. Mean BAC was 0.082% (range =0.047-0.100), roughly equivalent to 3-4 (male) or 2-3 (female) standard drinks. Alcohol was compared with either a placebo/pseudoplacebo (*k*=3) or an inactive control (*k*=6). Overall study quality scores ranged from 10 to 12 (*M*=10.83, *SD*=0.75).

3.3 Meta-analysis: Pain threshold

Meta-analysis indicated an overall analgesic effect of alcohol versus control, with significantly higher pain threshold recorded following alcohol administration, g=0.35, CI_{95}[0.17, 0.54], z=3.75, p=.002, representing a small analgesic effect[9]. Figure 2 depicts a forest plot of the 13 individual pain threshold comparisons, and shows that only one comparison reported increased pain (i.e., reduced pain threshold) in the alcohol condition, with 12 comparisons reporting decreased pain.

-- FIGURE 2 ABOUT HERE --

3.4 Meta-analysis: Pain intensity ratings

Meta-analysis indicated significantly reduced pain intensity ratings (k=9) following alcohol administration, g=0.64, CI_{95}[0.37, 0.91], z=4.71, p<.0001, representing a moderate to large[9] analgesic effect. A forest plot of the 9 individual comparisons is shown in Figure 3. As pain intensity was rated on a homogenous 11-point scale in all studies, where 0=no pain and 10=maximum pain, meta-analysis was repeated on the raw (unstandardized) ratings. Results were, naturally, consistent with analysis of the standardized difference (Mean Difference=1.25, CI_{95}[0.70, 1.80], z=4.45, p < .0001), and indicated a decrease from 5.30 (no-alcohol) to 4.05 (alcohol) points , or a reduction of 1.25 points or a decrease of approximately 22%.

Although analysis was performed on independent samples of participants, several studies were carried out by the same research laboratories, inviting the possibility of data dependency (e.g., due to a common methodology). Meta-analysis was accordingly rerun including laboratory as a second-order random factor[43], with a common coding given to comparisons obtained from the same laboratory. In line with the fairly wide distribution of effects sizes from the same laboratories illustrated in Figure 3, this additional analysis indicated no systematic effect of research laboratory and no substantive change in effect size or confidence intervals (g=0.61, CI_{95}[0.37- 0.85], p<.0001).

-- FIGURE 3 ABOUT HERE --

3.5 Sensitivity analysis

Rerunning meta-analysis replacing imputed correlations of r=0.75 with r=0.30 - 0.90 produced summary effect sizes ranging from g=0.29-0.39 for pain threshold and g=0.61-0.69 for pain intensity. This result suggests choice of imputed correlation had minimal impact on the effect size estimates. A minimal increase in effect size from the original g=0.35 for pain threshold was observed when excluding Führer and Hammer[22], g=0.39, which used atypical pain induction, and Chapman et al.[8], g=0.38, which reported semi-IQRs rather than SDs.

3.6 Publication bias

A suggestion of asymmetry in the funnel plot of pain threshold was confirmed by Egger's test (p=0.019), indicating potential publication bias. Trim and fill estimates produced a revised effect size estimate of g=0.31, CI_{95}[0.09-0.53], p=.005, compared to the original estimate of g=0.35. No obvious asymmetry was evident in the funnel plot of pain intensity with Egger's test non-significant, p=.27.

3.7 Meta-regression

Significant heterogeneity emerged for pain threshold (Q=31.61, df=12, p=.002; I^2=65%; τ=0.26) and pain intensity (Q=42.57, df=8, p < .001; I^2=79%; τ=0.35), with the values of I^2 suggesting moderate to high effect size inconsistency across

studies. Therefore, meta-regression analyses were conducted to identify potential moderators.

3.7.1 *Study quality*

Effect size was not moderated by overall quality ratings or use of subject/experimenter blinding for pain threshold and pain intensity, or randomization/counterbalancing for pain threshold, *p's*=.10-.54. Only one within-group study of pain intensity[20] reported no counterbalancing (with the no-alcohol condition always occurring first), so moderation analysis could not be reliably performed. Nevertheless, it is interesting to note that this study yielded the only negative study effect size for pain intensity (g=-0.13).

3.7.2 *Primary moderator: alcohol concentration and drinking frequency*

To examine whether alcohol analgesia was amplified for higher alcohol concentrations, meta-regression was performed with BAC as a moderator. For pain threshold, increasing BAC was significantly associated with increased analgesia, B=5.50, CI_{95}[0.03, 10.96], p=.048. For pain intensity, one study outlier with a high externally studentized residual[65] of z=3.84 was excluded, with its removal being further justified by this being the only study failing to employ counterbalancing[20]. Subsequent analysis found that higher BAC was significantly associated with increased analgesia, i.e., decreased pain ratings, B=9.84, CI_{95}[2.64, 17.04], k=11, p=.007. As a BAC of .02 roughly corresponds to one standard drink[67], regression coefficients were rescaled and indicated that every one standard drink resulted in an increase in Hedge's g of .11, CI_{95}[0.01, 0.22],

for elevated pain threshold and .20, CI_{95}[0.05, 0.34] for reduced pain intensity. A moderator plot of BAC against effect size for pain intensity is shown in Figure 4.

Values of pseudo-R^2 indicated that variation in study BAC accounted for 65% of heterogeneity in pain intensity ratings and 25% of heterogeneity in pain threshold, leaving relatively low (I^2=34%) and moderate (I^2=52%) levels of effect size inconsistency in each measure respectively. Drinking frequency (mean weekly alcohol consumption) was not examined as a moderator due to insufficient data[33].

-- FIGURE 4 ABOUT HERE --

3.7.3 *Other moderators*

Alcohol was associated with increased analgesia in studies with a higher proportion of males for pain threshold (*k*=9, *B*=0.006, *p* =.005) but not for pain ratings (*k*=9, *p*=.36). After rerunning this analysis controlling for BAC, gender composition remained significant (*p* =.043), suggesting any heightened analgesic effect in studies with more males was not a product of any differences in alcohol concentrations. Time interval between alcohol and pain stimulation, type of control group, stimulus modality, method of administration and familial alcoholism did not moderate alcohol effects for either pain outcome (*k*= 9-14, *p*=.34 to .93).

4 Discussion

To the best of our knowledge, the current study is the first meta-analysis to investigate the pain-relieving effects of alcohol assessed in controlled experimental studies. Eighteen studies of healthy individuals were examined, which provided data for 13 pain threshold comparisons (alcohol *n*=182, control *n*=182) and 9 pain intensity comparisons (alcohol *n*=174, control *n*=129). Several key findings emerged supporting an analgesic effect of alcohol: (1) Overall pain threshold was elevated following alcohol administration, although the magnitude of this effect was small (standardized mean difference=0.35); (2) Ratings of pain intensity were reduced after alcohol administration, with a moderate to large effect (*SMD*=0.64) observed; (3) A dose-response relationship emerged, with every .02% increment in Blood Alcohol Content or BAC (roughly equivalent to one standard drink) associated with heightened analgesia for both pain threshold (*SMD* increase=0.11) and pain intensity (*SMD* increase=.20).

Primary experimental studies investigating alcohol analgesia have yielded inconsistent findings, exemplified by the fact that only around half of the individual pain threshold studies in the current review were significant in and of themselves. The use of small samples and methodological variation, especially in alcohol dosage, are likely to contribute to this inconsistency and have led to uncertainty in establishing whether, and to what extent, alcohol produces relief from pain. The current study represents the first meta-analysis of these studies and provides robust evidence for the analgesic effects of alcohol. The reliability of these findings is endorsed by the use of sound experimental procedures (counterbalancing, subject/experimenter blinding, etc.) by most of the reviewed

studies and with effect sizes seemingly robust to suboptimal study quality. Furthermore, analgesic effects are unlikely to be attributable to participant expectancy bias, as effect sizes were similar for placebo (negligible alcohol dosage to reproduce taste and smell) and standard control comparisons. Pain dampening effects of alcohol were also unaffected by method of alcohol administration (oral/intravenous), type of pain stimulation and family history of alcoholism. Although some evidence suggested that analgesic effects for pain threshold may be amplified in males, this finding should be treated extremely cautiously given both the exploratory nature of the analysis and that only a limited number of studies included female participants. Nevertheless, this preliminary finding may have important ramifications and warrants further empirical investigation in primary research.

4.1 Strength of analgesic effects and implications

While analgesic effects of alcohol were relatively weak for pain threshold, moderate-large effects emerged for ratings of pain intensity at .08% BAC (3-4 standard drinks for males and 2-3 for females), and this was amplified at higher BAC (although analgesic efficacy cannot be ascertained outside of the study data range of 0.03-0.11% BAC). These results mimic those typically seen for opiates where more pronounced analgesia is observed for suprathreshold levels of pain[58].

The fact that alcohol analgesia was observed for moderate pain, with a mean pain intensity rating of 5.3/10 for the studies reviewed here, may have implications for typical real-world pain experienced outside of the laboratory.

Pain intensity ratings of 5/10 approximate several types of acute pain responses, e.g., soft tissue injury and post-operative pain[26] and chronic pain conditions[6], and represent the threshold at which pain has a serious impact on functioning in cancer pain[37]. Moreover, the reduction of 1.25 points on the 0-10 point scale meets the definition of a minimal clinically important difference (MCID) of 0.9/10 (or 9/100) used by several authors[48]; although MCID thresholds as high as 3/10 have also been suggested[52]. In addition, analgesic effects of alcohol on pain intensity are comparable to opiods for chronic pain, with SMD=.60 reported in a meta-analytic review[23]. Collectively, these findings suggest that alcohol may be an effective analgesic for non-laboratory pain. However, it is important to emphasize that clinical pain differs from experimental pain on a number of key dimensions[58] and although suggestive, the analgesic effects observed for experimental pain cannot be generalized to clinical pain states without further rigorous empirical investigation.

One clinical implication of the current findings is that the analgesic properties of alcohol are likely to contribute to the increased usage of alcohol observed in pain patients[40,45]. Alcohol dependence may develop based on negative reinforcement models of drug addiction[68], with pain relief representing the reinforcement, and maintenance encouraged by the hyperalgesia that follows analgesia after alcohol withdrawal[25]. Alcohol is also easily accessible and relatively inexpensive and this is likely to further encourage its use as an analgesic in preference to alternative drugs of abuse or more difficult to obtain treatments. However, excessive alcohol consumption can present significant threats to long-term health, demonstrating associations with heart disease, liver disease, cancer mental health problems[70],

mortality[41] and an increased risk for developing future chronic pain conditions[17]. The current findings suggest that the level of alcohol consumption needed to provide sustained moderate to large analgesia for persistent or recurrent pain exceeds the World Health Organization's guidelines of <20g ethanol (less than two standard drinks) a day[24]. In addition, continued analgesia may require increasing levels of consumption given that tolerance to alcohol's analgesic effects with repeated exposure has been demonstrated in rats and is also likely to occur in humans[25]; although a lack of available data on average weekly alcohol consumption in the current review precluded an empirical investigation of this possibility. As such, efforts to promote alternative pain management strategies (e.g. physical therapy, exercise, controlled use of pain medication) with fewer long-term health consequences may prove extremely beneficial. At the same time, the analgesic effects of alcohol may also provide leads for the search of less toxic and non-addictive forms of analgesia.

An additional, experimental implication is that alcohol consumption should be restricted prior to pain testing to optimize reliability of pain assessment. Although alcohol elimination is affected by several factors, such as gender and bodyweight[67], an abstinence period of 5 hours may constitute a reasonable practical guideline, as .10% BAC will reduce to approximately .02% BAC (approx. one standard drink) after this time[67].

4.2 Mechanisms of action

Although analgesic mechanisms cannot be determined from the current data, animal models suggest that alcohol may inhibit nociceptive transmission

centrally via non-opioid pathways by binding to N-methyl-D-aspartate (NMDA) receptors at the spinal cord level in mice[38,50], and similar mechanisms could be present in humans. Alternatively, analgesia could be mediated by the anxiolytic properties of alcohol[55,69], although this possibility has received limited empirical evaluation. Clearly, future research is required to disentangle the mechanisms through which alcohol confers an analgesic effect, which could serve as a lead to novel treatments for pain.

4.3 Limitations

The current meta-analysis was restricted to studies investigating response to noxious stimuli (especially electrical) in healthy participants and this represents a notable limitation. Clinical pain differs from experimentally-induced pain on both psychological (e.g. affect, perceived controllability)[49] and physical (e.g. duration, central sensitization)[58] components, which may limit the clinical generalizability of the current findings. Nevertheless, if alcohol analgesia is partially mediated through emotional blunting, it may be that analgesia is actually enhanced for clinical pain states given the greater negative affect produced by these states. An additional limitation is that a lack of available data on average alcohol consumption precludes conclusions on whether analgesic effects are attenuated by previous or chronic alcohol exposure.

4.4 Future Studies

Despite these limitations, the current findings provide strong support for substantive analgesic effects of alcohol on acute pain based on laboratory studies, which provide a level of control not easily achievable in clinical research

and which help establish causality. Further research is needed to determine clinical generalizability, and additional insights may be gained with the use ischemic and dermal capsaicin experimental pain models that evoke several aspects of clinical pain whilst preserving experimental control[58]. In addition, the inclusion of an anxiety measure in both experimental and clinical studies would permit an examination of the extent to which alcohol analgesia is mediated by its anxiolytic effects. Finally, future studies should routinely assess average alcohol consumption to estimate whether analgesic efficacy is diminished with sustained alcohol use, and assess the impact of variables such as pain duration, intensity and age which have been suggested to affect the efficacy of other analgesics[58].

4.5 Conclusions

To the authors' knowledge, this is the first meta-analysis to examine the effect of alcohol on experimentally-induced pain. Results provide robust evidence that alcohol is an effective analgesic for short-term pain, with small effects observed for pain threshold and moderate to large effects for ratings of pain intensity that exceed the threshold for clinical significance. These findings provide support for alcohol analgesia as a possible mechanism for promoting alcohol dependence in people with persistent pain and could help explain the relationship between alcohol use and chronic pain. Further research is needed to corroborate these findings in clinical pain states and to assess how the mechanisms of alcohol-related analgesia could be harnessed to develop novel, less toxic and non-addictive pain treatments.

5 Acknowledgements

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Figure captions

Figure 1. PRISMA flow diagram.

Figure 2. Forest plot for pain threshold.

Figure 3. Forest plot for pain intensity ratings.

Figure 4. Pain intensity: Study effect size by BAC (point sizes proportional to study weights)

Table 1. Characteristics of included studies

Study	Study Design	N Total	N - Alcohol group or condition	N Control Group or condition	Alcohol Administration	Population	Pain induction	Mean Blood Alcohol Content %	Pain Measure	Quality Assessment Rating
Arout et al, 2016[3]	W	18	18	18	intravenous	NFH	chemical	0.04 0.10	pain threshold	11
Ralevski et al, 2010-a[55]	W	31	31	31	intravenous	NFH	electric	0.04 0.10	pain threshold pain tolerance	12
Ralevski et al, 2010-b[55]	W	17	17	17	intravenous	FH	electric	0.04 0.10	pain threshold pain tolerance	12
Duarte et al, 2008[12]	W	8	8	8	drink	NFH	pressure	0.084	pain threshold intensity ratings	11
Fuhrer et al, 2008[22]	W	9	9	9	intravenous	NFH	chemical pressure	NA	pain threshold	7
Zacny et al, 1998[71]	W	11	11	11	drink	NFH	cold pressor	0.031 0.062	intensity ratings	11
Stewart et al, 1995[59]	PP	81	63	18	drink	mixed	electric	0.063 0.085 0.088	intensity ratings discomfort ratings	12
Lau et al, 1994[44]	W	17	17	17	drink	NFH	electric	0.11	pain threshold	7
Finn et al, 1990-a[21]	W	12	12	12	drink	FH	electric	0.09	intensity ratings	11
Finn et al, 1990-b[21]	W	12	12	12	drink	NFH	electric	0.09	intensity ratings	11
Gustafson et al, 1989[31]	B	24	12	12	drink	NFH	electric	0.058	pain threshold intensity ratings discomfort ratings	10
Gustafson et al, 1988[29]	W	8	8	8	drink	NFH	electric	0.076	pain threshold intensity ratings discomfort ratings	8

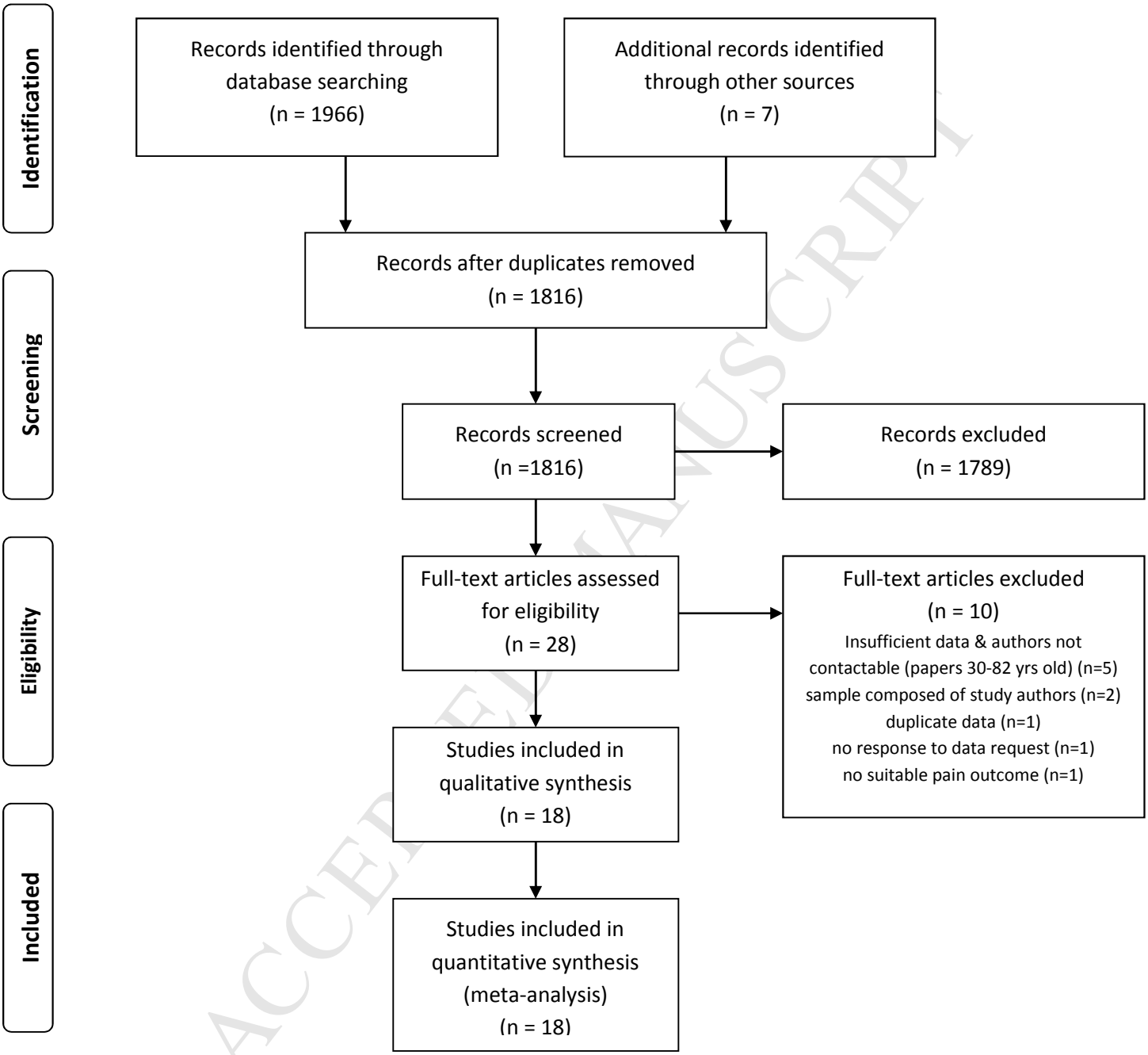
Study	Study Design	N Total	N - Alcohol group or condition	N Control Group or condition	Alcohol Administration	Population	Pain induction	Mean Blood Alcohol Content %	Pain Measure	Quality Assessment Rating
Woodrow et al, 1988[69]	W	14	14	14	drink	NFH	pressure	0.07	pain threshold pain tolerance	10
Finn et al, 1988[20]	W	20	20	20	drink	FH	electric	0.078	intensity ratings discomfort ratings	10
Cutter et al, 1987[10]	W	20	20	20	drink	NA	cold pressor	0.06	intensity ratings	10
Finn et al, 1987-a[19]	W	12	12	12	drink	NFH	electric	0.10	intensity ratings discomfort ratings	11
Finn et al, 1987-b[19]	W	12	12	12	drink	FH	electric	0.09	intensity ratings discomfort ratings	11
Finn et al, 1987-c[19]	W	12	12	12	drink	FH	electric	0.10	intensity ratings discomfort ratings	11
Gustafson et al, 1985[30]	B	36	18	18	drink	NFH	electric	0.067	pain threshold intensity ratings discomfort ratings	9
Saddler et al, 1985[57]	W	8	8	8	intravenous	NFH	pressure	0.087	pain threshold	10
James et al, 1978[36]	W	7	7	7	intravenous	NFH	pressure	0.11	pain threshold	7
Chapman et al, 1965[8]	W	15	15	15	drink	NFH	heat	.07[§]	pain threshold	6
Total	W=19, PP=1, B=2	404	356	311	drink=16, intravenous=6	NFH=16, FH=5, mixed=1	electric=13, pressure=5, cold=2, chemical=2, heat=1	Mean BAC=.078%	threshold=13, tolerance=3, intensity =13, discomfort =8	Mean=9.9

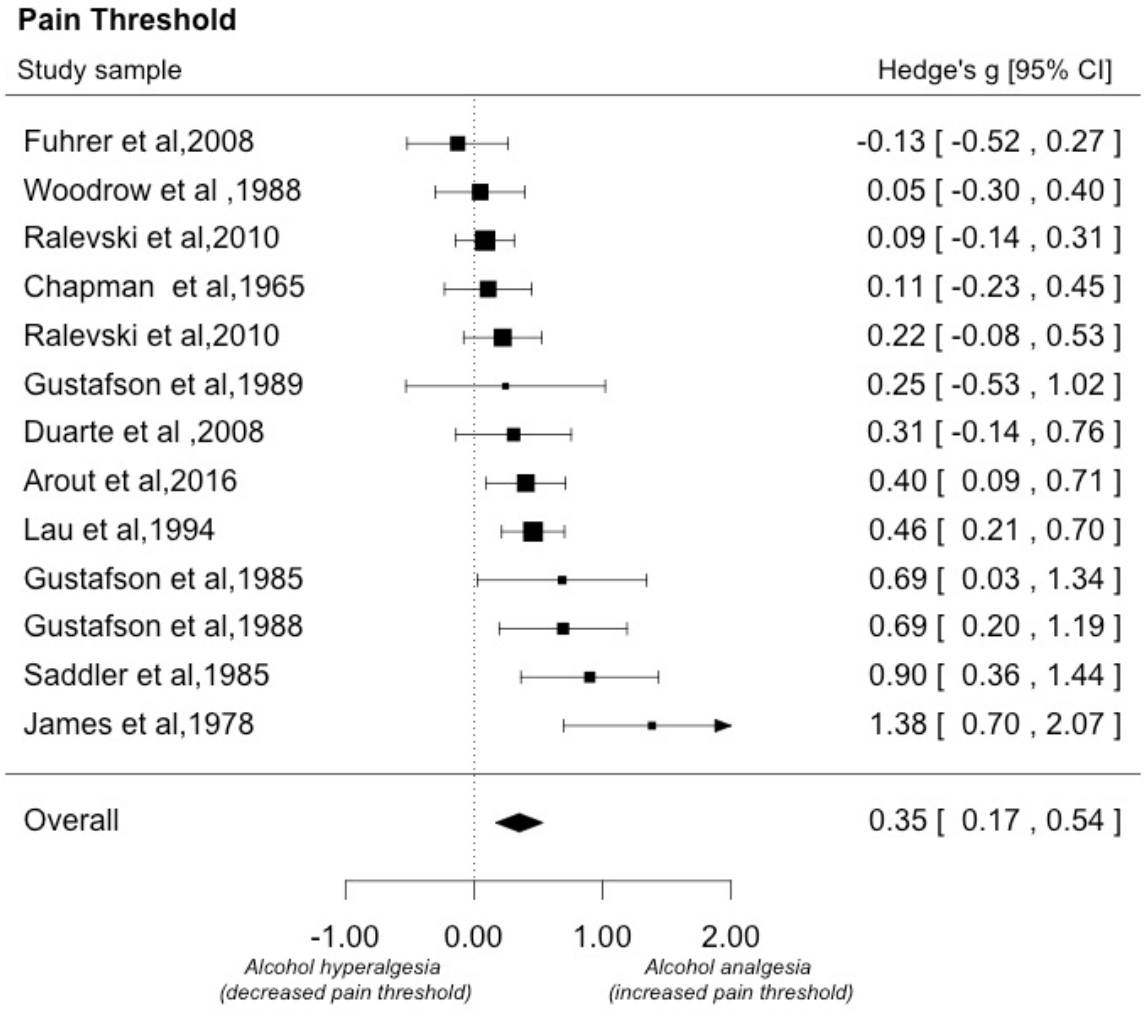
Key: Study design: W= within groups; B=Between Groups; PP=pre-post (pre-post in alcohol and placebo groups); Population: NFH= no family history of alcoholism; FH= family history of alcoholism

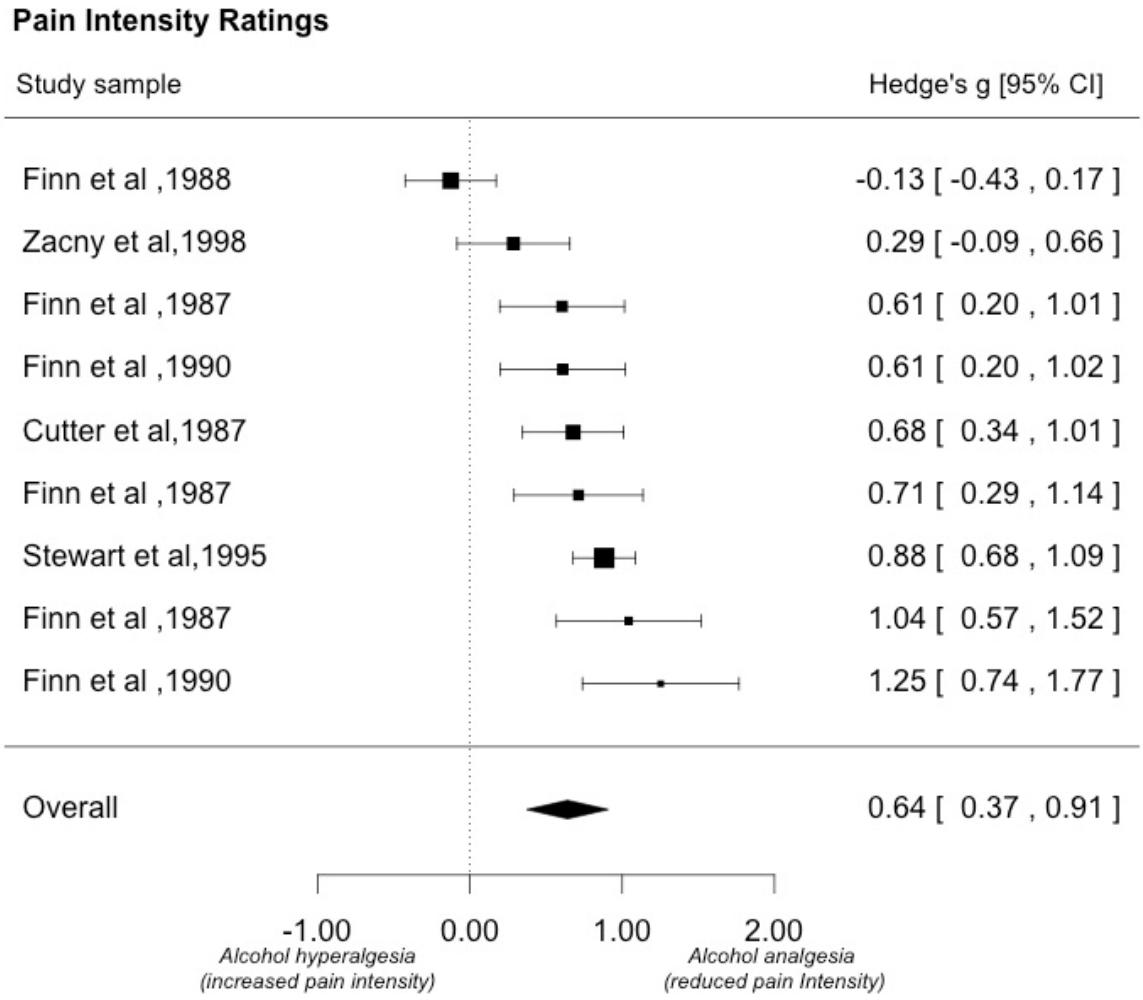
[§]Estimated using Widmark equation

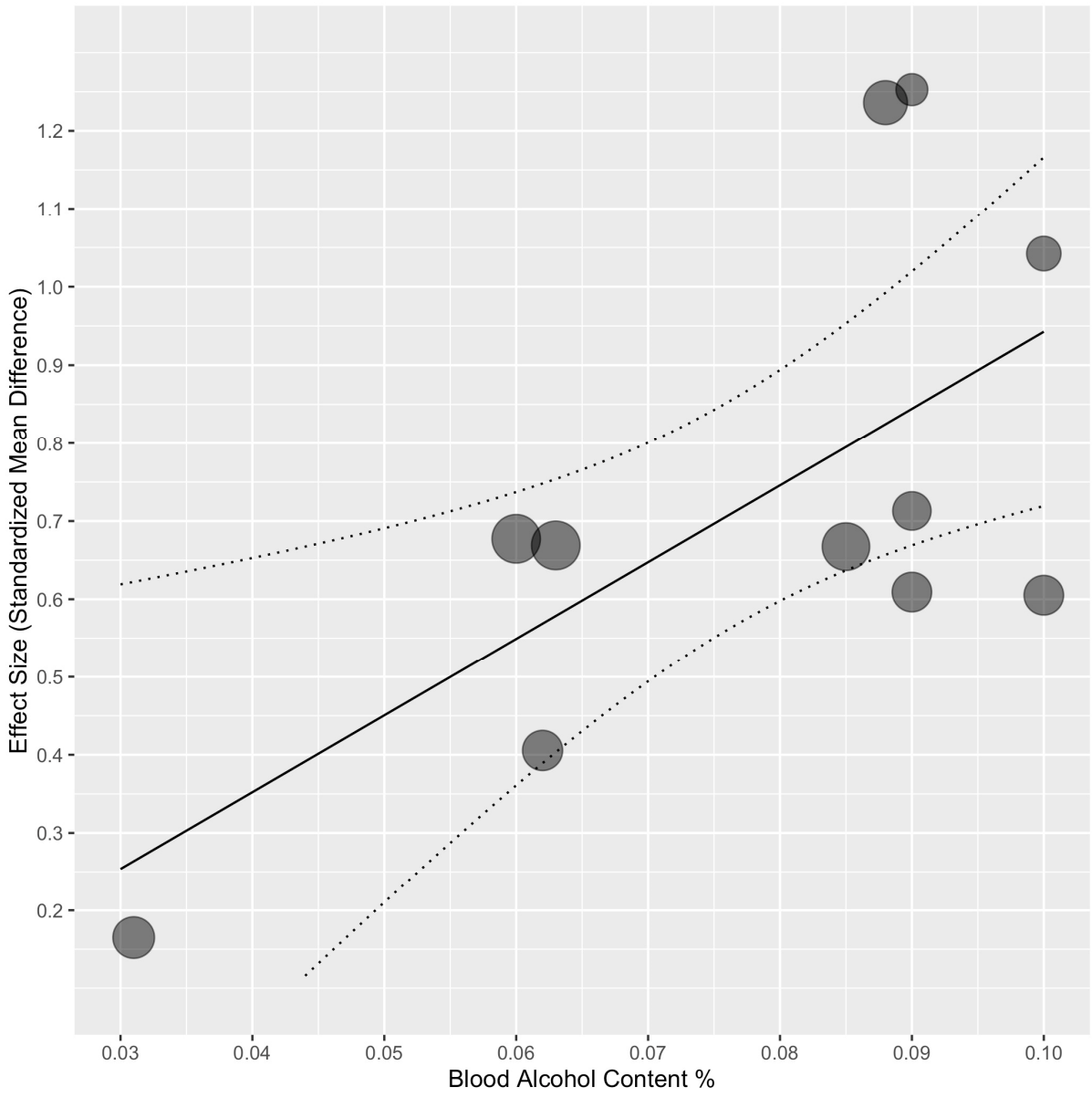
Hyphenated letters (-a,-b,-c) suffixed to reference indicates different subsample data within study

Figure 1. Prisma flow diagram – alcohol pain studies




Pain Threshold
Study sample
Hedge's g [95% CI]
Fuhrer et al,2008
-0.13 [-0.52 , 0.27]
Woodrow et al ,1988
0.05 [-0.30 , 0.40]
Ralevski et al,2010
0.09 [-0.14 , 0.31]
Chapman et al,1965
0.11 [-0.23 , 0.45]
Ralevski et al,2010
0.22 [-0.08 , 0.53]
Gustafson et al,1989
0.25 [-0.53 , 1.02]
Duarte et al ,2008
0.31 [-0.14 , 0.76]
Arout et al,2016
0.40 [0.09 , 0.71]
Lau et al,1994
0.46 [0.21 , 0.70]
Gustafson et al,1985
0.69 [0.03 , 1.34]
Gustafson et al,1988
0.69 [0.20 , 1.19]
Saddler et al,1985
0.90 [0.36 , 1.44]
James et al,1978
1.38 [0.70 , 2.07]
Overall
0.35 [0.17 , 0.54]
-1.00
0.00
1.00
2.00
Alcohol hyperalgesia
(decreased pain threshold)
Alcohol analgesia
(increased pain threshold)


Pain Intensity Ratings
Study sample
Hedge's g [95% CI]
Finn et al ,1988
-0.13 [-0.43 , 0.17]
Zacny et al,1998
0.29 [-0.09 , 0.66]
Finn et al ,1987
0.61 [0.20 , 1.01]
Finn et al ,1990
0.61 [0.20 , 1.02]
Cutter et al,1987
0.68 [0.34 , 1.01]
Finn et al ,1987
0.71 [0.29 , 1.14]
Stewart et al,1995
0.88 [0.68 , 1.09]
Finn et al ,1987
1.04 [0.57 , 1.52]
Finn et al ,1990
1.25 [0.74 , 1.77]
Overall
0.64 [0.37 , 0.91]
-1.00
0.00
1.00
2.00
Alcohol hyperalgesia
(increased pain intensity)
Alcohol analgesia
(reduced pain Intensity)



Highlights

- Meta-analysis of 18 controlled experiments supported anagelsic effects of alcohol
- Small increase in pain threshold, moderate-large decrease in pain ratings
- Higher blood alcohol linearly related to greater analgesia
- Analgesic effects may account for alcohol dependence in those with persistent pain

Online Supplementary Material

Appendix S1. Search terms.
(ethanol OR alcohol) AND ((pain OR nocicept*) OR (analgesi* OR analgesic OR analgetic)) AND (Ischemi* OR pressure OR mechanical OR chemical OR capsaicin OR cold OR heat OR thermal OR reflex OR electric*) AND "humans"[MeSH Terms] AND English[lang]

Online Supplementary Material

Appendix S2. Quality assessment ratings for each study.

	Items													
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Total**
Arout et al, 2016	1	0	1	1	1	1	1	1	1	0	1	1	1	11
Ralevski et al, 2010	1	0	1	1	1	1	1	1	1	1	1	1	1	12
Duarte et al, 2008	1	0	1	1	1	1	1	1	0	1	1	1	1	11
Fuhrer et al, 2008	1	1	1	1	1	1	1	0	0	0	1	0	1	9
Zacny et al, 1998	1	0	1	1	1	1	1	1	1	0	1	1	1	11
Stewart et al, 1995	1	0	1	1	1	1	1	1	1	1	1	1	1	12
Lau et al, 1994	1	0	1	1	1	1	1	1	0	1	0	0	1	9
Finn et al, 1990	1	0	1	1	1	1	1	1	1	1	0	1	1	11
Gustafson et al, 1989	1	0	1	1	1	1	1	1	1	1	0	0	1	10
Gustafson et al, 1988	1	0	1	1	0	1	1	1	1	1	0	0	1	9
Woodrow et al, 1988	1	0	1	1	0	1	1	0	1	1	1	1	1	10
Finn et al, 1988	0	0	1	1	1	1	1	1	1	1	0	1	1	10
Cutter et al, 1987	1	0	1	1	1	1	1	0	1	0	1	1	1	10
Finn et al, 1987	1	0	1	1	1	1	1	1	1	1	0	1	1	11
Gustafson et al, 1985	1	0	1	1	1	1	1	0	0	1	1	0	1	9
Saddler et al, 1985	1	0	1	1	0	1	1	0	1	1	1	1	1	10
James et al, 1978	1	0	1	0	0	1	1	0	0	1	1	0	1	7
Chapman et al, 1965	0	0	1	1	0	1	1	0	1	1	0	0	0	6
Mean score	0.89	0.06	1.00	0.94	0.72	1.00	1.00	0.61	0.72	0.78	0.61	0.61	0.94	9.89

Key: item 1: Were subjects randomly allocated to groups (in a within-subjects design, was order randomized or counterbalanced)?; item 2: Was there a description of all participants who did not complete study measures?; item 3: Were study objectives defined clearly?; item 4: Were the outcome measures defined clearly?; item 5: Was there a clear description of the inclusion and exclusion criteria?; item 6: Was there a clear description of the interventions (i.e., pain procedure and alcohol administration procedure)?; item 7: Was there at least one control (comparison) group?; item 8: Were all relevant participant characteristics described? (i.e., mean age, sex, drinking history, health); item 9: Were complete outcome data reported (i.e., point measures and measures of variability)?; item 10: Were outcome data reported non-selectively?; item 11: Was there blinding of subjects?; item 12: Was there blinding of experimenters?; item 13: Were relevant baseline measurements obtained - i.e., recording of blood alcohol levels?